

**Practitioner's Docket No.: 868\_012**

*PATENT*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI

Serial No.: 10/587,320 Group Art Unit: 1618

Filed: May 10, 2007 Examiner: Nissa M. Westerberg

Conf. No.: 4731

For: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

## REQUEST FOR RECONSIDERATION

Sir:

In response to the Office Action mailed March 10, 2010, Applicants respectfully request reconsideration and withdrawal of the rejections of record based on the following arguments. Claims 10-12, 14, 18, 20 and 21 are pending herein.

Claims 10-12, 14 and 18-21 [sic., 18, 20-21] stand newly rejected under §103(a) over Mylari in view of Crary (newly cited), and under §103(a) over Akita in view of Crary and Wani. The rejections are similar to those in the past Office Action, but differ in the citation of Crary, which is alleged by the Examiner to show that selenium has been used for treating and preventing macular edema in diabetic

retinopathy. The Examiner concludes from such a teaching that the claimed invention would have been obvious to one of ordinary skill in the art based upon the collective teachings in the references. Applicants respectfully disagree.

Applicants point out that there is no chemical relationship between the ARIs shown in the primary references to Mylari and Akita, and the selenium-vitamin E combination in Crary. Applicants respectfully submit that the Examiner clearly has resorted to hindsight to justify the rejections, because the rejections are not chemically supportable.

The arguments presented by Applicants during the course of prosecution, particularly in the replies of July 29, 2009 and February 26, 2010, explain at great length with reliance upon publications and the submitted Declarations of both Dr. Lorenzi and Mr. Kato, that the art had no reason to expect that a compound such as SNK-860 would be useful in the treatment of diabetic macular edema. The Examiner accepted those arguments and evidence by virtue of the fact that the prior rejections were withdrawn. The Examiner has now applied the newly cited reference to Crary, but that reference deals with a composition that is clearly not chemically related to the compounds disclosed in the primary references or the active compound recited in the present claims.

The Examiner asserts that Crary teaches that an agent for diabetic retinopathy (DR) is useful for diabetic macular edema (DME). But, Crary merely discloses an efficacy for DME in patients with DR (see patient 1; column 3, lines 23-26 and patient 4; column 4, lines 7-10) and DME in patients with DME (see patient 2; column 3, lines 46-49 and patient 3; column 3, lines 2-5 from the bottom) by supplementing a

composition comprising selenium and vitamin E. There is no disclosure of a relationship between an efficacy for DR and that for DME. In Crary, benefit of short-term treatment (approximately 1 month) for DME is clearly reported, but there is no mention of efficacy for DR.

It was reported more than a decade ago that therapy evaluation of a medicament for DR needs long term administrations of the medicament to patients (see attached Ref. 1, Ref. 2, and Ref. 3) and the FDA concludes that therapy evaluation of a medicament for DR needs administrations of the medicament to patients for more than three years (see attached Ref. 4, p. 482: Fig. 2) based on Ref. 1. Crary also described that the efficacy for DR was achieved by treatment for three years (see column 3; lines 34-36 (patient 1)).

Thus, a person of ordinary skill in the art has understood, since the 1990s, that therapy evaluation of a medicament for DR needs long term administrations of the medicament to patients. Therefore, a person of ordinary skill in the art would think it is impossible to evaluate the effectiveness of selenium and vitamin E on DR in just a month of administrations as done in Crary.

Meanwhile, it is notable that Clary distinguishes precisely between DR and DME, since his description separates DME in patients with DR (patient 1 and 4) from DME in patients with DME (patient 2 and 3).

As mentioned above, there are some questions posed by what is discussed in Crary. Crary discloses that a composition comprising selenium and vitamin E is a diet supplement for diabetes (e.g., Abstract lines 2-6). Based on the teaching of Crary, a person skilled in the art would understand that a composition comprising selenium and

vitamin E has ameliorated DME, one of diabetic complications, by ameliorating diabetes mellitus, but would never understand that an agent effective in the treatment of DR is also effective in the treatment of DME as the Examiner asserts.

In support of Applicants' position, see attached Ref. 5 as evidence. The reference discloses that vitamin E is a supplement effective in the treatment of diabetes, and by administering vitamin E to a diabetic patient, blood glucose and HbA1c are lowered and diabetes mellitus is ameliorated (p. 1435, left paragraph, Results: lines 4-7 and lines 11-15). A person of ordinary skill in the art understands that lowering of blood glucose and HbA1c leads to amelioration of diabetes mellitus, which leads to amelioration of diabetic complications. The evidence is widely accepted by the international community and can be understood theoretically. Therefore, a person of ordinary skill in the art realizes that the effects of selenium and vitamin E on DME, one of diabetic complications, are derived from the amelioration of diabetes mellitus by blood glucose and HbA1c lowering effects of vitamin E. A person of ordinary skill in the art would not therefore conclude that an agent effective in the treatment of DR is also effective in the treatment of DME.

In contrast, SNK-860 does not have lowering effects on HbA1c in a diabetic patient as described in attached Ref. 6 (p. 1777, right paragraph, Change in HbA1c, lines 1-10). In other words, as SNK-860 is an agent for ameliorating diabetic complications, but not for ameliorating diabetes mellitus itself, the case of SNK-860 is fundamentally different from that of Crary. Efficacy of SNK-860 for DME cannot be predicted by replacing selenium and vitamin E in Crary with SNK-860.

In addition, for the sake of argument, let us say Crary discloses the efficacy of the composition comprising selenium and vitamin E for DR. Applicants address the case in which three pieces of information exist. The first piece of information is that agent A is effective for DR and DME. The second piece of information is that agent B is effective for DME, but not effective for DR. The third piece of information is that therapeutic methods of DR and DME are different from each other. Here, the first piece of information is in Crary, the second piece of information is in attached Ref. 7, submitted previously, and the third piece of information is common technical knowledge in the art. A person of ordinary skill in the art could surmise that an agent could be effective for both diseases incidentally based on the first and second pieces of information, but because of the third piece of information, that person would not think that an agent effective in the treatment of DR is always effective in the treatment of DME, as well.

It is unequivocal that Crary does not suggest that an agent effective in the treatment of DR is also effective in the treatment of DME. Consequently, the combination of Crary and any of the other references fails to teach or even remotely suggest the present invention to one skilled in the art. Therefore, the rejection should be reconsidered and withdrawn.

If the Examiner believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, the Examiner is herein requested to call Applicants' attorney at the phone number noted below.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

June 8, 2010

Date

Respectfully submitted,

Stephen P. Burr  
Reg. No. 32970

SPB/CW/tlp

Attachments:

Ref. 1 - DCCT Research Group, "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus," *N Engl J Med* 1993;329:977-986.

Ref. 2 - U.K. Prospective Diabetes Study (UKPDS) Group, "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS33)," *Lancet* 1998;352:837-853.

Ref. 3 - Ohkubo Y, et al., "Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study," *Diabetes Res Clin Pract* 1995;28:103-117.

Ref. 4 - Csaky KG, et al., "Report from the NEI/FDA ophthalmic clinical trial design and endpoints symposium," *Invest Ophthal Vis Sci* 2008;479-489.

Ref. 5 - Paolisso G, et al., "Daily vitamin E supplements improve metabolic control but not insulin secretion in elderly type II diabetic patients," *Diabetes Care* 1993;16:1433-1437.

Ref. 6 - Hotta N, et al., "Clinical efficacy of fidarestat, a novel aldose reductase inhibitor, for diabetic peripheral neuropathy," *Diabetes Care* 2001;24:1776-1782.

Ref. 7 - The PKC-DRS Study Group, "The Effect of Ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy," *Diabetes* 2005;54:2188-2197.

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